

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, CO_2R^{13} , $O(C=OR^{13})$, SO_2R^{14} , SOR^{14} , $(C=O)NR^{13}R^{14}$, or $NR^{14}(C=O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1 - C_6 alkyl and C_3 - C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, C_1 - C_4 alkyl and benzyl;

(ii) an oligopeptide of 1 to 5 amino acids or a peptidomimetic molecule having substantially similar binding properties as the oligopeptide;

(iii) C_3 - C_6 cycloalkyl, C_6 - C_{10} bicycloalkyl, C_3 - C_7 cycloalkylmethyl, or C_7 - C_{10} arylalkyl, which may be additionally substituted with R^{11} as defined above;

R_3 is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, C_1 - C_{12} hydrocarbon chain or $O-C_1-C_{12}$ hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

(i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy or halogen;

(ii) hydrogen; and

(iii) C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_3 - C_7 cycloalkenyl, or C_1 - C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) hydroxy, halogen, C_1 - C_4 haloalkyl, or C_1 - C_4 haloalkoxy;

(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, $C_1[.]C_3$ alkylsulfonyl, or sulfone; and

(iii) $C_1[.]C_3$ alkyl which may be additionally substituted with at least one R^{11} as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

alternatively Z' and R_1 collectively form a ring system selected from the group consisting of:

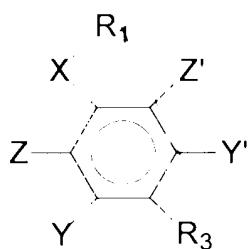
(a) C_5-C_8 carbocyclic ring which may be saturated or unsaturated, and which may be additionally substituted with at least one R^{11} as defined above; and

(b) C_5-C_{10} heterocyclic ring system which may be saturated or unsaturated and which includes at least one nitrogen, oxygen or sulfur atom, and which may be additionally substituted with at least one R^{11} as defined above;

and pharmaceutically acceptable salts thereof; with the proviso that when $X-R_1$ is a fluorinated keto acyl, Z is hydrogen.

12. (Once Amended) [The] A method [of] according to claim 8, wherein the picornavirus species is a rhinovirus species.

13. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species,] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is $-C=O$;

R_1 is $-CF_3$;

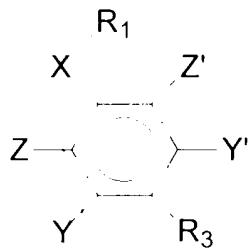
Z and Z' are hydroxyl, except when $X-R_1$ is a fluorinated keto acyl group, Z must be hydrogen;

R_3 is hydrogen; and

Y and Y' are selected from the group consisting of $-Cl$, $-I$, $-Br$, $-CF_3$, $-F$, $-CN$, $-COOH$, $-SO_3H$, $-SO_2NH_2$ and $-CONH_2$; and

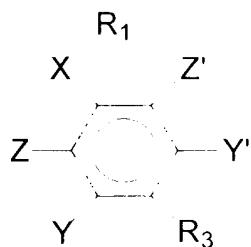
and Z' and R_1 cannot form a ring.]

14. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species,] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



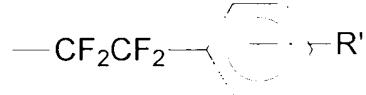
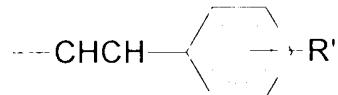
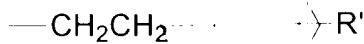
wherein X is $-C=O$;
 R_1 is $-CF_3$;
Z is hydroxyl, except when $X-R_1$ is a fluorinated keto acyl group, Z must be hydrogen;
 Z' and R_3 are hydrogen; and
Y and Y' are selected from the group consisting of $-Cl$, $-I$, $-Br$, $-CF_3$, $-F$, $-CN$, $-COOH$, $-SO_3H$, $-SO_2NH_2$ and $-CONH_2$; and
and Z and R_1 cannot form a ring.]

15. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species,] inhibiting picornaviral replication in a subject, wherein said compound



has the formula:

wherein X is $-C=O$;
 R_1 is H , $-CH_3$, $-CF_3$, $CH_3-CH_2-CH_2-CH_2-$, CH_3-CH_2- , $CH_3-CH_2-CH_2-$,
 $CF_3-CF_2-CF_2-CF_2-$, $-NH-R''$ or one of the following phenyl groups



wherein R' is $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, or $-\text{COCH}_3$ and R'' is $-\text{OH}$, $-\text{NH}_2$, $-\text{OCH}_3$ and $-\text{OCH}_2\text{CH}_3$;

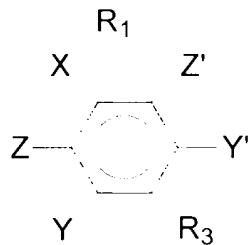
Z and Z' are hydroxyl, except when X-R₁ is a fluorinated keto acyl group, Z must be hydrogen;

R₃ is hydrogen; and

Y and Y' are $-\text{CF}_3$ [; and

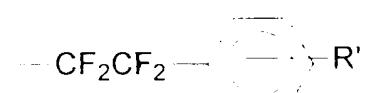
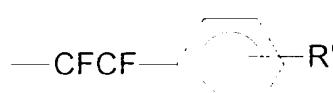
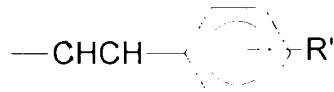
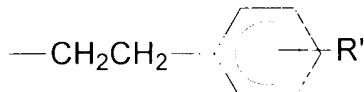
and Z' and R₁ cannot form a ring.]

16. (Twice Amended) A method for [the treatment of a disease caused by a picornavirus species,] inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is $-\text{C}=\text{O}$;

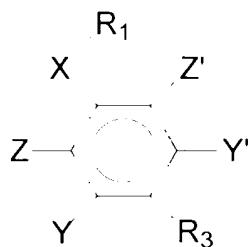
R₁ is H, $-\text{CH}_3$, $-\text{CF}_3$, $\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---}$, $\text{CH}_3\text{---CH}_2\text{---}$, $\text{CH}_3\text{---CH}_2\text{---CH}_2\text{---}$, $\text{CF}_3\text{---CF}_2\text{---CF}_2\text{---CF}_2\text{---}$, $-\text{NH}-\text{R}''$, or one of the following phenyl groups



wherein R' is -OH, -NH₂, -COOH, or -COCH₃ and R'' is -OH, -NH₂, -OCH₃ and -OCH₂CH₃;

Z is hydroxyl, except when X-R₁ is a fluorinated keto acyl group, Z must be hydrogen;
 Z' and R₃ are hydrogen; and
 Y and Y' are -CF₃; [and
 and Z' and R₁ cannot form a ring.]

17. (Once Amended) A method [for the treatment of a disease caused by a picornavirus species.] of inhibiting picornaviral replication in a subject, wherein said [compound has] method includes the use of a compound with the formula:



X is selected from the group consisting of -C=O-, -S=O-, and -C=S-;

R₁ is selected from the group consisting of:

- (i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R¹¹, wherein R¹¹ is selected from the group consisting of:
 - (ia) C₁-C₄ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl, C₆-C₁₀ bicycloalkyl or aryl which may be substituted or unsubstituted;
 - (ib) halogen, cyano, nitro, amino, hydroxy, adamantlyl, carbamyl, carbamyoxy or keto;
 - (ic) an oligopeptide of 1-3 amino acid residues; and
 - (id) NR¹³R¹⁴, COR¹³, O(C=OR¹³), SO₂R¹⁴, SOR¹⁴, (C=O)NR¹³R¹⁴, or NR¹⁴(C=O)R¹³;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1 - C_6 alkyl, and C_3 - C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, C_1 - C_4 alkyl and benzyl;

R_3 is selected from the group consisting of:

(i) phenyl, hydroxyl, C_1 - C_{12} hydrocarbon chain and $O-C_1-C_{12}$ hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl, and NHR^{11} , wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

(i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy, and halogen;

(ii) C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_3 - C_7 cycloalkenyl and C_1 - C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) halogen, C_1 - C_4 haloalkyl, and C_1 - C_4 haloalkoxy;

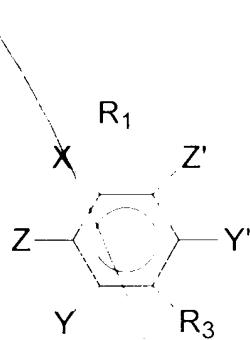
(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C_1 - C_3 alkylsulfonyl, and sulfone; and

(iii) C_1 - C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

and pharmaceutically acceptable salts thereof; with the proviso that when $X-R_1$ is a fluorinated keto acyl, Z is hydrogen.

18. (New Claim) -- A method of inhibiting picornaviral replication in a subject, comprising the step of administering an effective amount of a compound having a formula:



wherein

5 X is selected from the group consisting of C=O, S=O, C=S, (C=O)-NH, (C=O)-O and (C=O)-S;

R₁ is selected from the group consisting of:

10 (i) hydrogen, hydroxyl or a hydrocarbon chain [of] from [about] 1 to about 10 carbons long selected from the group consisting of saturated, unsaturated and fluorinated, wherein said hydrocarbon chain is unsubstituted or substituted with at least one R¹¹, wherein R¹¹ is selected from the group consisting of:

(ia) C₁-C₄ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl, C₆-C₁₀ bicycloalkyl or aryl which may be substituted or unsubstituted;

15 (ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyoxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

20 (id) NR¹³R¹⁴, CO₂R¹³, O(C=OR¹³), SO₂R¹⁴, SOR¹⁴, (C=O)NR¹³R¹⁴, or NR¹⁴(C=O)R¹³;

wherein:

25 R¹³ is selected from the group consisting of hydrogen, phenyl, benzyl, C₁-C₆ alkyl and C₃-C₆ alkoxyalkyl; and

R¹⁴ is selected from the group consisting of hydrogen, hydroxyl, C₁-C₄ alkyl and benzyl;

30 (ii) an oligopeptide of 1 to 5 amino acids or a peptidomimetic molecule having substantially similar binding properties as the oligopeptide;

(iii) C₃-C₆ cycloalkyl, C₆-C₁₀ bicycloalkyl, C₃-C₇ cycloalkylmethyl, or C₇-C₁₀ arylalkyl, which may be additionally substituted with R¹¹ as defined above;

35 R₃ is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, C₁-C₁₂ hydrocarbon chain or O-C₁-C₁₂ hydrocarbon chain which may be additionally substituted with at least one R¹¹ as defined above; and

40 (ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulphydryl, amino, carboxyl and NHR¹¹, wherein R¹¹ is defined as above;

Z' is selected from the group consisting of:

45 (i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy or halogen;

(ii) hydrogen; and

(iii) C₁-C₄ alkyl, C₁-C₄ alkenyl, C₃-C₇ cycloalkenyl, or C₁-C₃ alkoxy which may be additionally substituted with at least one R¹¹ as defined above;

Y and Y' are independently selected from the group consisting of:

50 (i) hydroxy, halogen, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, or hydrogen except that Y and Y' cannot be hydrogen simultaneously;

(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C₁-C₃ alkylsulfonyl, or sulfone; and

55 (iii) C₁-C₃ alkyl which may be additionally substituted with at least one R¹¹ as defined above; and

(iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic;

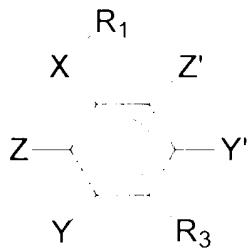
alternatively Z' and R₁ collectively form a ring system selected from the group consisting of:

(a) C₅-C₈ carbocyclic ring which may be saturated or unsaturated, and which may be additionally substituted with at least one R¹¹ as defined above; and

60 (b) C₅-C₁₀ heterocyclic ring system which may be saturated or unsaturated and which includes at least one nitrogen, oxygen or sulfur atom, and which may be additionally substituted with at least one R¹¹ as defined above;

and pharmaceutically acceptable salts thereof; with the proviso that when X-R₁ is a fluorinated keto acyl, Z is hydrogen.

19. (New Claim) -- A method of inhibiting picornaviral replication in a subject, wherein said method includes the use of a compound with the formula:



5 X is selected from the group consisting of -C=O-, -S=O-, and -C=S-;

R₁ is selected from the group consisting of:

(i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R¹¹, wherein R¹¹ is selected from the group consisting of:

(ia) C₁-C₄ alkyl, C₂-C₄ alkenyl, C₃-C₈ cycloalkyl, C₆-C₁₀

10 bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyoxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) NR¹³R¹⁴, COR¹³, O(C=OR¹³), SO₂R¹⁴, SOR¹⁴, (C=O)NR¹³R¹⁴, or NR¹⁴(C=O)R¹³;

15 wherein:

R¹³ is selected from the group consisting of hydrogen, phenyl, benzyl, C₁-C₆ alkyl, and C₃-C₆ alkoxyalkyl; and

20 R¹⁴ is selected from the group consisting of hydrogen, hydroxyl, C₁-C₄ alkyl and benzyl;

R₃ is selected from the group consisting of:

(i) phenyl, hydroxyl, C₁-C₁₂ hydrocarbon chain and O-C₁-C₁₂ hydrocarbon chain which may be additionally substituted with at least one R¹¹ as defined above; and

25 (ii) an oligopeptide of 1 to 3 amino acids, an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, amino, carboxyl, and NHR¹¹, wherein R¹¹ is defined as above;

Z' is selected from the group consisting of:

30 (i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy, and halogen;
(ii) C₁-C₄ alkyl, C₁-C₄ alkenyl, C₃-C₇ cycloalkenyl and C₁-C₃ alkoxy which may be additionally substituted with at least one R¹¹ as defined above;

Y and Y' are independently selected from the group consisting of:

35 (i) halogen, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, or hydrogen except that Y and Y' cannot be hydrogen simultaneously;
(ii) carbamyl, carbamido, cyano, keto, vinyl, sulfoxide, nitro, C₁-C₃ alkylsulfonyl, and sulfone; and
(iii) C₁-C₃ alkyl which may be additionally substituted with at least one R¹¹ as defined above; and
40 (iv) an oligopeptide of 1 to 3 amino acids or a peptidomimetic; and pharmaceutically acceptable salts thereof; with the proviso that when X-R₁ is a fluorinated keto acyl, Z is hydrogen. --

REMARKS

Claims 8 and 12-17 are pending in the application. Applicants have amended claims 8 and 12-17, and added new claims 18-19.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 8 AND 12-17

The Examiner has rejected claims 8 and 12-17 on the grounds that they are not enabled by the specification. The Examiner has suggested amendments to these claims to overcome the §112, first paragraph rejections. Claims 8 and 12-17 have been amended according to the Examiner's suggestion. Therefore, it is respectfully submitted that such claims are patentable, having overcome this rejection.